ORIGINAL ARTICLE

# Autologous stem cell transplantation in the treatment of multiple myeloma with 17p deletion

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**KEY WORDS**

autologous stem cell transplantation, multiple myeloma, 17p deletion

**ABSTRACT**

**INTRODUCTION** Deletion of chromosome 17p [del(17p)] in patients with multiple myeloma is associated with a poor prognosis. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains the standard of treatment in this population.

**OBJECTIVES** The aim of the study was to compare the treatment outcomes with high-dose chemotherapy and ASCT with standard treatment in patients with del(17p).

**PATIENTS AND METHODS** We collected data from 12 Polish centers between 2011 and 2017. The records of 97 patients with p53 deletion were assessed, including 29 individuals treated with ACST and 68 receiving standard treatment alone.

**RESULTS** During the follow-up, 45 patients died and the overall survival (OS) for the whole group was 33 months (range, 1–66 months), with a median progression-free survival (PFS) of 13 months (range, 1–46 months). The prognostic factors of OS in a multivariable analysis were calcium levels at diagnosis within the reference range (hazard ratio [HR], 0.24; 95% CI, 0.12–0.48) and at least partial remission achieved after the first-line treatment (HR, 0.25; 95% CI, 0.12–0.51). Treatment with ASCT was an important factor in improving survival (HR, 3.23; 95% CI, 1.52–6.84). Abnormal kidney function at the time of diagnosis reduced the PFS (HR, 0.46; 95% CI, 0.22–0.94). When the analysis was limited only to patients who could be candidates for ASCT, the survival benefit of the procedure was lost ($P = 0.21$).

**CONCLUSIONS** Patients with multiple myeloma with del(17p) do not benefit from high-dose chemotherapy followed by ACST.

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**INTRODUCTION** Deletion of chromosome 17p [del(17p)] is found in 10% of newly diagnosed patients with multiple myeloma (MM), with a higher prevalence in more advanced disease.[1-3] Its presence is associated with a poor prognosis and resistance to chemotherapy.[4,5] These patients tend to present with relatively frequent extramedullary and central nervous system involvement.[6-8] The International Myeloma Working Group (IMWG) currently recommends fluorescence in situ hybridization (FISH) as the standard approach to identification of the primary genetic event.[9] Currently, there is no consensus on the appropriate FISH-positivity cutoff value for defining the presence of del(17p), and the minimum percentage of del(17p)-positive cells associated

## WHAT'S NEW?

Autologous stem cell transplantation (ASCT) is a standard of treatment for younger patients with multiple myeloma. It is based on administration of high-dose chemotherapy followed by stem cell support. However, it is known that patients with a confirmed deletion of chromosome 17p do not respond to any chemotherapy. Therefore, it is unclear why they should respond to chemotherapy given in very high doses. In our opinion, misleading information originates from studies that included all patients with high-risk disease independently of underlying genetic abnormalities. Our data obtained by fluorescence in situ hybridization confirmed that ASCT does not provide an expected benefit for patients, and it can even be potentially harmful.

with a poor prognosis is unknown.[10] Thesignificance of the p53 mutation in MM is probably associated with a poor prognosis but requires additional research, and at present, it can be used only in the context of clinical trials.[3,9] To treat patients with high-risk cytogenetics, including patients with del(17p), the IMWG recommends bortezomib-based induction followed by high-dose therapy with double ASCT and posttransplant bortezomib maintenance.[9] This recommendation is based mostly on the results of the HOVON-65/GMMG-HD4 trial (Dutch-Belgian Cooperative Trial Group for Hematology Oncology Group-65 / German-speaking Myeloma Multicenter Group-HD4).[11]

The role of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains controversial. The clinical outcome in patients treated with novel drugs compared with a matched control group without p53 deletion showed significantly worse survival in the del(17p) group.[12] However, because there are limited data from stratified clinical trials, high-dose chemotherapy followed by double ASCT is still recommended as a standard approach in this high-risk population of patients.[9]

In this study, we analyzed real-world data from MM patients with del(17p) treated with or without ASCT. We aimed to assess the effectiveness of high-dose chemotherapy with ASCT in the context of this high-risk genetic abnormality.

**PATIENTS AND METHODS** We collected data on patients with confirmed del(17p) on the basis of FISH results. Data were obtained from 12 Polish centers by searching hospital records, including cytogenetic laboratory results, from 2011 through 2017. The FISH analysis was performed at the participating centers from fresh bone marrow aspirates using probes containing DNA sequences that were specific to the p53 gene and mapped to the 17p13.1 region of chromosome 17. A cutoff value of 20% of cells was used to confirm FISH positivity. Demographic data and information on disease characteristics, treatment regimens, and clinical endpoints of patients receiving standard chemotherapy and those on high-does chemotherapy with ASCT are summarized in TABLE 1. Initially, the standard first-line treatment for all patients was cyclophosphamide or melphalan, thalidomide, and dexamethasone, and the second-line treatment was bortezomib, cyclophosphamide and thalidomide, and dexamethasone. The latter was the first-line treatment since 2015. The initial treatment was similar in the standard-chemotherapy and ASCT groups: a thalidomide-only regimen was administered in 42% and 46% of patients, respectively; a bortezomib-only regimen, in 30% and 29%; and a combined bortezomib and thalidomide regimen, in 19% and 20%. Abnormal kidney function was defined as a creatinine level of higher than 2 mg/dl (176 μmol/l), according to the Durie–Salmon staging system.[13]

Prognostic features and treatment response were assessed according to the IMWG Uniform Response Criteria.[14] The characteristics of patients undergoing ASCT are presented in TABLE 2. The median time to transplant was 373 days (range, 176–1040 days). Posttransplant analysis was performed on day 100 for patients treated with ASCT. Because only 3 patients received maintenance therapy, no separate analysis was performed in this group.

**Ethics approval** All patients provided written informed consent to participate in the study. The approval of the ethics committee was not required at the time of the study.

**Statistical analysis** Overall survival (OS) was calculated from the time of diagnosis to the time of death, using the Kaplan–Meyer method. For progression-free survival (PFS), death or progression was considered an event. The Pearson $\chi^2$ and Fisher tests were used to compare differences between categorical variables. The rank-sum test was used to compare the distribution of continuous variables. A Cox proportional hazard regression analysis was applied to compare OS and PFS between groups to identify risk factors in patients who underwent the ASCT and those treated with standard chemotherapy only. Factors found to be significant at a $P$ level of 0.2 were then included in a multivariable analysis. To determine the effect of treatment on survival, a proportional hazards regression analysis was carried out, which included the treatment group adjusted for other prognostic factors. All $P$ values were 2 sided. Because we did not use an accelerated failure time model, conclusions about shorter or longer survival are indirect. Analyses were performed using the Statistica 13.1 software (2016, Dell Inc, Tulsa, Oklahoma, United States).

**RESULTS** We collected data from 97 patients with the p53 deletion, of whom 29 were treated with ASCT as part of their initial treatment. The remaining 68 patients received standard treatment without high-dose chemotherapy. During the follow-up, 45 patients died and the OS for the total group was 33 months (range, 1–66 months) with a median PFS of 13 months (range, 1–46 months; FIGURES 1 and 2).

**TABLE 1** Characteristics of the whole study group, patients receiving standard chemotherapy, and those receiving high-dose chemotherapy followed by autologous stem cell transplant

| Parameter | | All patients (n = 97) | Chemotherapy + ASCT (n = 29) | Standard chemotherapy (n = 68) | *P* value (ASCT vs chemotherapy) |
|---|---|---|---|---|---|
| Age, y, median (range) | | 63 (38–84) | 59 (38–67) | 64.5 (43–84) | <0.001 |
| Sex, n (%) | Female | 42 (43) | 14 (48) | 28 (41) | 0.19 |
| | Male | 55 (57) | 15 (52) | 40 (59) | |
| Myeloma subtype, n (%) | IgG | – | 15 (52) | 32 (47) | 0.27 |
| | IgA | – | 9 (31) | 18 (26) | – |
| | Light-chain only | – | 3 (10) | 16 (24) | – |
| | Nonsecretory | – | 2 (7) | 1 (1) | – |
| Light chain type, n (%) | Kappa | 56 (58) | 17 (59) | 39 (57) | – |
| | Lambda | 35 (36) | 10 (34) | 25 (37) | 0.86 |
| | Unknown | 6 (6) | 2 (7) | 4 (6) | – |
| Creatinine level at diagnosis, n (%) | Normal | 71 (73) | 25 (86) | 46 (68) | 0.06 |
| | Increased | 26 (27) | 4 (14) | 22 (32) | – |
| Calcium level at diagnosis, n (%) | Normal | 67 (63) | 20 (69) | 47 (69) | 0.97 |
| | Increased | 30 (31) | 9 (31) | 21 (31) | – |
| Osteolytic lesions, n (%) | Yes | 88 (91) | 62 (91) | 26 (90) | 0.81 |
| | No | 9 (9) | 6 (9) | 3 (10) | – |
| $\beta_2$-microglobulin, mg/l, median (range) | | 4.95 (1.2–49.7) | 3.9 (1.2–17.8) | 9.0 (1.5–49.7) | <0.001 |
| ISS, n (%) | 1 | 28 (29) | 11 (38) | 7 (10) | <0.001 |
| | 2 | 29 (30) | 11 (38) | 18 (26) | – |
| | 3 | 34 (35) | 2 (7) | 32 (47) | – |
| | Unknown | 16 (16) | 5 (17) | 11 (16) | – |
| Best response to the initial treatment, n (%) | sCR | 1 (1) | 1 (3) | – | <0.001[a] |
| | CR | 12 (12) | 6 (21) | 6 (9) | – |
| | VGPR | 23 (24) | 13 (45) | 10 (15) | – |
| | PR | 25 (26) | 7 (24) | 18 (26) | – |
| | SD | 3 (3) | – | 3 (4) | – |
| | PD | 22 (23) | 2 (7) | 20 (29) | – |

a sCR + CR + VGPR + PR vs PD

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; IgA, immunoglobulin A; IgG, immunoglobulin G; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

**Autologous stem cell transplant** In the group receiving high-dose chemotherapy with ASCT, 22 patients (93%) responded to the initial standard treatment, achieving at least partial remission (PR) at the time of transplant (TABLE 1). Progressive disease was noted in only 1 patient, and 1 patient progressed from PR to complete remission (CR) as a result of the second-line treatment. During the study, 11 deaths were reported. The median OS was 42 months (range, 9–68 months; FIGURE 1), and the median PFS was 12 months (range, 2–46 months; FIGURE 2). Six patients underwent double transplant (TABLE 2). There was no difference in OS between the single- and double-transplant group (HR, 0.43; 95% CI, 0.17–1.12).

**Standard-treatment group** Among patients who achieved CR (9%) at the end of the first-line treatment, very good partial response (VGPR) was noted in 10 (15%), PR in 18 (27%), and the remaining 23 patients (34%) were assessed as having stable and progressive disease. Data from 11 patients (16%) were missing or were not assessed. There were 34 deaths in this group. The median OS was 13 months (range, 1–49 months; FIGURE 1), and the median PFS was 4 months (range, 1–19 months; FIGURE 2).

**Univariable and multivariable analysis** A univariable analysis was performed to determine significant prognostic factors. The following factors were nonsignificant: age >65 or >70 years, the type of heavy and light chain, presence of osteolytic lesions, or the type of first-line treatment including thalidomide, bortezomib, or both. The significant prognostic factors for OS included normal or increased creatinine levels (HR, 0.37; 95% CI, 0.20–0.68); normal or increased calcium levels (HR, 0.3; 95% CI, 0.17–0.55); response to initial treatment: progressive disease/stable disease vs PR, VGPR, CR, or stringent CR (HR, 0.24; 95% CI, 0.13–0.47); and initial treatment with or without

**TABLE 2** Characteristics of autologous stem cell transplantation

| Parameter | | Value |
|---|---|---|
| Transplant | Single | 22 (76) |
| | Tandem | 7 (24) |
| Conditioning regimen (first transplant) | MEL200 | 24 (83) |
| | MEL140 | 5 (17) |
| Results of the first transplant | sCR | 1 (3) |
| | CR | 7 (24) |
| | VGPR | 12 (41) |
| | PR | 7 (24) |
| | PD | 1 (3) |
| | Missing/not assessed | 1 (3) |
| Conditioning regimen (second transplant) | MEL200 | 6 (71.4) |
| | Other | 2 (28.6) |
| Results of the second transplant | CR | 4 (50) |
| | VGPR | 2 (25) |
| | PR | 2 (25) |

Data are presented as number (percentage) of patients.

Abbreviations: MEL140, melphalan 140 mg/m$^2$ of body surface; MEL200, melphalan 200 mg/m$^2$ of body surface; others, see TABLE 1

ASCT (HR, 3.22; 95% CI, 1.52–6.82). Only 1 factor (abnormal kidney function at diagnosis) was significant for PFS (HR, 0.46; 95% CI, 0.22–0.94).

The following 3 factors remained significant for OS in the multivariable analysis: no increase in the calcium level at diagnosis (HR, 0.24; 95% CI, 0.12–0.48); minimum PR achieved as a result of the first-line treatment (HR, 0.25; 95% CI, 0.12–0.51); and worse prognosis seen in patients without ASCT as part of the initial treatment (HR, 3.22; 95% CI, 1.52–6.83).

Next, we investigated whether patients benefited from high-dose chemotherapy, so only potential candidates for ASCT were included in the analysis. When the comparison was limited only to patients who obtained at least PR as a result of the initial treatment and were 70 years old or younger, a survival benefit in transplant recipients was no longer observed ($P$ = 0.21).

**DISCUSSION** Despite considerable progress in the treatment of MM, adverse genetic risk continues to have a significant impact on survival. This applies particularly to patients with del(17p). However, the first question is how del(17p) should be defined. The cutoff values up to 60% from a single cell were accepted in different studies.[15,16] Also, the cutoff value related to the FISH positivity has been recently discussed in detail.[17] However, there is no consensus on the appropriate cutoff value for defining the presence of del(17p). In our study, the cutoff of 20% was set based on standard criteria that were in use during the study period. Additionally, the optimal management of this group of patients remains controversial.[18] Recently, the cancer clonal fraction threshold of 0.55 for patients with the *TP53* mutation or deletion was reported as the best method to identify a high-risk population.[19] However, we did not include patients with the *TP53* mutation in our study. Among patients with del(17p), only 18 had a cancer clonal fraction higher than 0.55. No difference was found between the group with a threshold of >0.2 and that with <0.55 and >0.55, most probably due to a very small population.

Chang et al[20] did not confirm the effectiveness of ASCT in genetic high-risk groups, including individuals with del(17p). The IFM 2005–01 trial, which compared bortezomib plus dexamethasone versus vincristine, doxorubicin, and dexamethasone followed by auto-ASCT, failed to confirm the benefit of the new treatment in a subgroup of patients with del(17p).[21] However, the current IMWG recommendation for the treatment of patients with high-risk cytogenetics, including patients with del(17p), is a prolonged bortezomib-based treatment followed by high-dose therapy with double ASCT.[11] This is based mostly on the results of the randomized phase III HOVON-65/GMMG-HD4 study, which assigned newly diagnosed symptomatic patients with MM to receive induction therapy with vincristine, doxorubicin, and dexamethasone or bortezomib, doxorubicin, and dexamethasone followed by high-dose melphalan and ASCT maintenance consisting of thalidomide or bortezomib for 2 years. A significant advantage of bortezomib-based treatment was observed in patients with the 17p13 deletion (median PFS, 12 months vs 22 months; median OS, 24 months vs not reached at 54 months; HR, 0.36; 95% CI, 0.18 to 0.74).

In a study by Shaughnessy et al,[22] 441 patients were treated with Total Therapy 3, which incorporated bortezomib, thalidomide, and dexamethasone induction followed by consolidation and maintenance treatment. In contrast to the previous Total Therapy 2, Total Therapy 3 results did not show any negative effect on the rate or duration of the CR or survival associated with the presence of p53 haploinsufficiency.[22] The benefit of bortezomib, thalidomide, and dexamethasone followed by double ASCT in this high-risk group was also observed in the GIMEMA study (Italian Group for Hematological Disease in Adults).[23] A recent meta-analysis by Liu et al[24] suggested an improved survival of patients with del(17p) if they were treated with a combination of carfilzomib or elotuzumab and lenalidomide or pomalidomide with dexamethasone followed by bortezomib maintenance.

The recommendation for double ASCT is based on a meta-analysis of 4 European trials.[25] These studies include high-risk patient groups with del(17p) but also with translocation t(4; 14). The 4-year OS rate was 76% in the tandem-transplant group and 33% in patients who received only a single procedure. However, the advantage of tandem transplant in MM was not confirmed in prospective studies. In the Bologna 96 study, Cavo et al[26] observed higher CR rates after double ASCT (47% vs 33%, $P$ <0.01) in

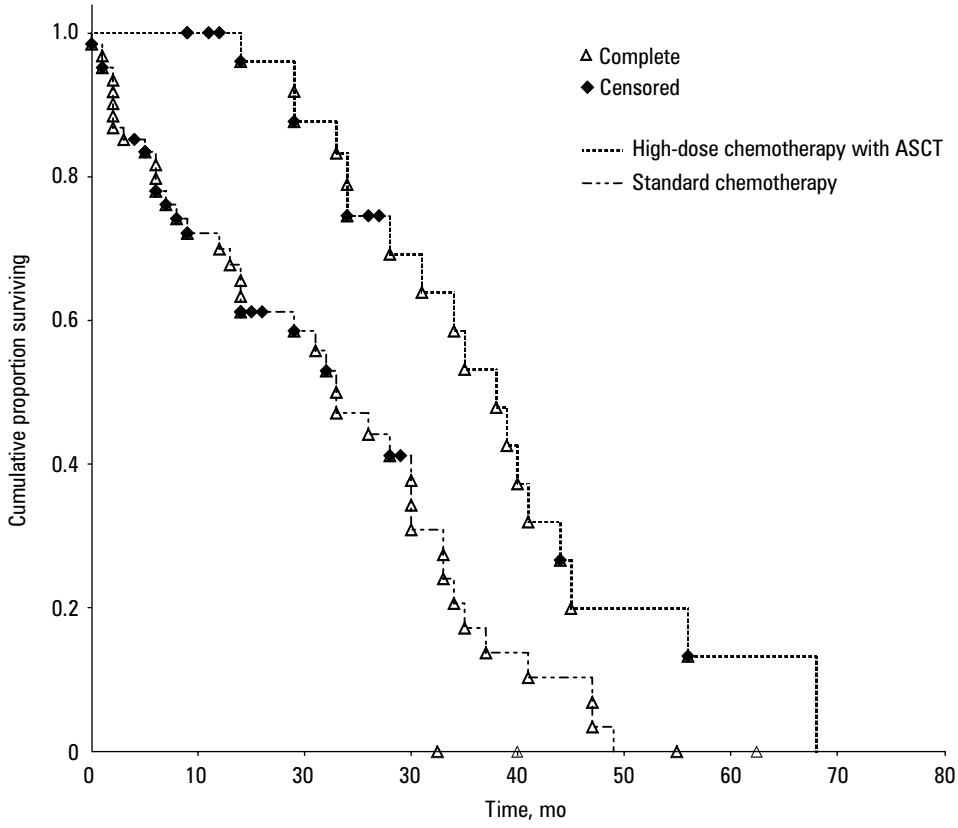


**FIGURE 1** Overall survival in patients treated with standard chemotherapy and high-dose chemotherapy with autologous stem cell transplantation (ASCT)

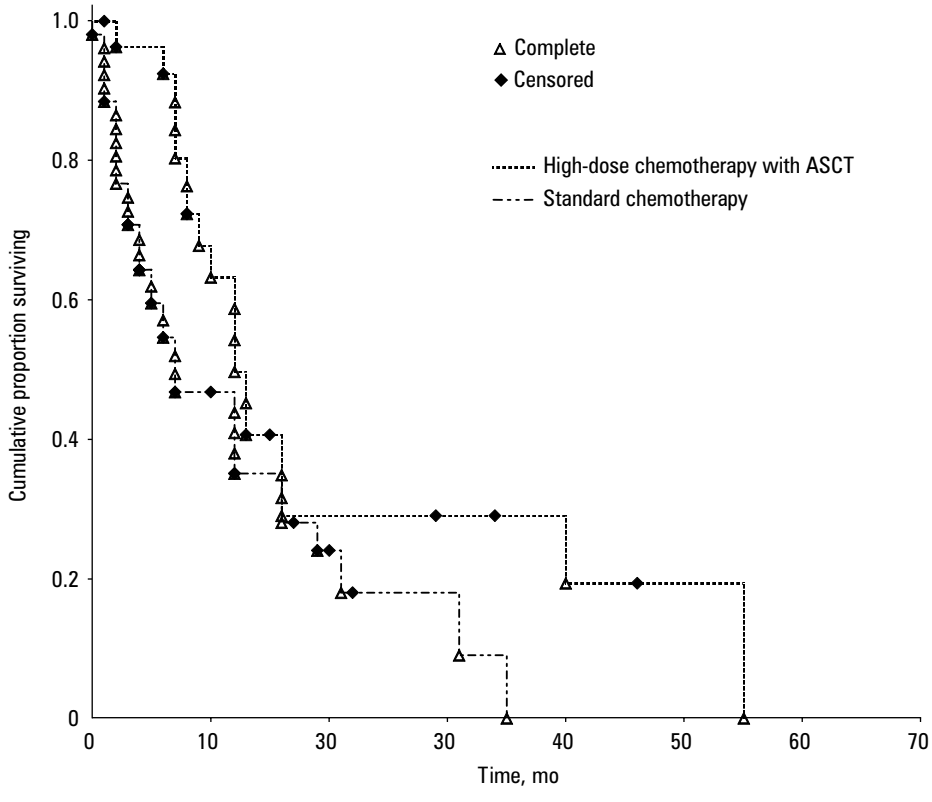


**FIGURE 2** Progression-free survival in patients treated with standard chemotherapy and high-dose chemotherapy with autologous stem cell transplantation (ASCT)

high-risk groups, but failed to show prolonged OS. There has been no prospective studies on the effectiveness of ASCT limited only to patients with del(17p13). In a case-matched study where patients with del(17p) were compared with standard-risk patients from the University of Texas MD Anderson Cancer Center database, no benefit of ASCT was found in patients who were initially treated with proteasome inhibitors or immunomodulatory drugs.[12]

Our study confirmed the poor prognosis in patients with del(17p). Similar to some other studies, our results did not corroborate previous findings on significant effectiveness of high-dose

treatment compared with standard therapy based on novel drugs. In a multicenter analysis from 8 centers in Israel, Cohen et al[27] noted improved survival after ASCT only in patients who were in remission for a minimum of 6 months. Kroger et al[28] showed that only the use of a combined tandem autologous–allogeneic transplantation can overcome the negative prognostic effect of del(17p13) in patients with complete molecular remission.

Apart from ASCT as part of treatment as well as response to the initial treatment, hypercalcemia was found to remain significant. This observation has been recently confirmed by Zagouri et al.[29] Additionally, there are extensive literature data on kidney failure as a risk factor for MM and ASCT.[30-33]

Our study confirms that ASCT has no benefit in MM. However, because of the limitation related to the retrospective design, this issue should be addressed in future prospective (possibly randomized) studies.

## ARTICLE INFORMATION

**CONTRIBUTION STATEMENT** JC and AJ conceived the concept of the study. JC analyzed the data. All authors were involved in data collection as well as edited and approved the final version of the manuscript.

**CONFLICT OF INTEREST** None declared.



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